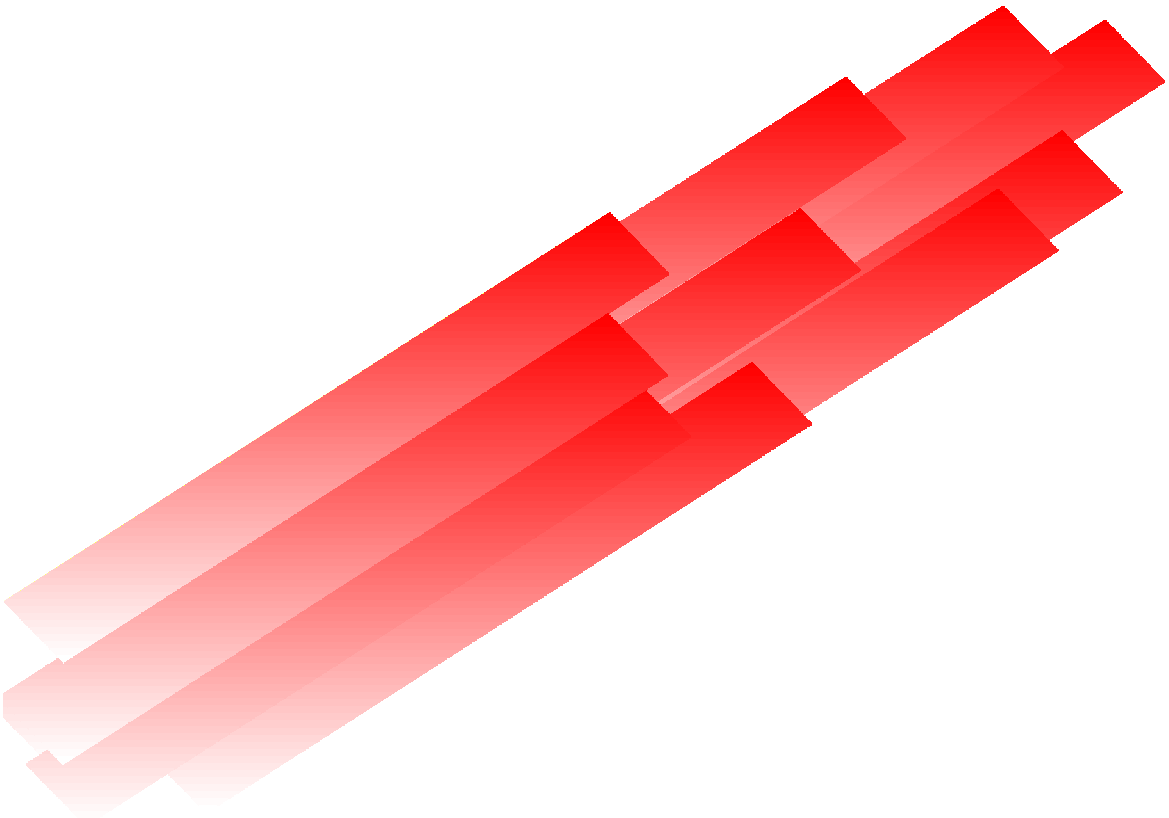
Guidance for Industry

Buspirone Hydrochloride Tablets In Vivo Bioequivalence and In Vitro DissolutionTesting



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
May 1998
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GUIDANCE FOR INDUSTRY[1]

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I. INTRODUCTION

This is revision 1 of the guidance for industry on in vivo bioequivalence and in vitro dissolution testing for buspirone hydrohloride tablets. The guidance has been revised to reflect the recent availability of buspirone hydrochloride tablets in 15 milligram (mg) dosage forms. Bioequivalence is tested using the highest available dosage of the reference listed drug. The guidance also notes the nonlinearity of buspirone at multiple-dosing.

A. Clinical Usage/Pharmacology

Buspirone hydrochloride is an antianxiety agent (1, 2). Clinically it is effective in the management of anxiety disorders or short-term relief of symptoms of anxiety. Buspirone has no anticonvulsant or muscle relaxant activity and has little sedative effect. It does not substantially affect psychomotor function (3, 4). There is no evidence that the drug causes either physical or psychological dependence (5). The mechanism of action of buspirone is not known. Some in vitro preclinical studies indicate that buspirone has high affinity for serotonin ($5\text{-}HT_{1A}$) receptors, and moderate affinity for brain D_2 receptors (5-9).

For the management of anxiety disorders, the usual initial adult dosage of buspirone is 10 to 15 milligrams (mg) daily, usually in two or three divided doses. Dosage is increased as

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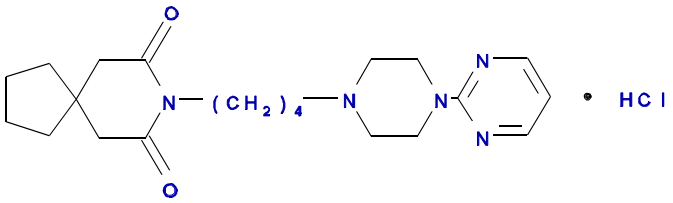
[1] This guidance has been prepared by the Biopharmaceutical Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on buspirone hydrochloride tablets in vivo bioequivalence and in vitro dissolution testing. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573.

necessary in increments of 5 mg daily to achieve an optimal therapeutic response. The maximum daily dose should not exceed 60 mg per day (5).

Buspirone is currently marketed by Bristol-Myers Squibb Company under the trade name Buspar in scored oral tablets of 5 mg, 10 mg, and 15 mg.

B. Chemistry

Buspirone hydrochloride is a white crystalline powder, soluble in water, with a molecular weight of 422. The chemical structure of buspirone is shown below:



C. Pharmacokinetics

Buspirone is rapidly and almost completely absorbed from the gastrointestinal (GI) tract. The drug undergoes extensive first-pass metabolism, with about 4 percent of a dose reaching the systemic circulation unchanged following oral administration (10,11). Following oral administration of a single dose of 20 mg in healthy volunteers, peak plasma buspirone concentrations of 1 to 6 nanograms (ng)/mL have been observed to occur within 40 to 90 minutes (5,12). Plasma concentrations of unchanged buspirone are low and exhibit substantial interindividual variation with oral administration of the drug (13). Approximately 95 percent of buspirone is bound to plasma proteins (14).

Buspirone is rapidly metabolized by oxidation to produce several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinylpiperazine (10,15). Because of rapid metabolism, less than 1 percent of the parent drug is excreted unchanged in the urine (10). The pharmacologically active metabolite has about 20 to 25 percent of anxiolytic activity of buspirone. In humans, blood concentrations of the active metabolite (1-PP) remain low even after chronic administration of buspirone. The contribution of 1-PP to the pharmacologic and/or toxic effect thus remains to be fully elucidated.

The average elimination half-life of unchanged buspirone after single doses of 10 to 40 mg is reported to be two to three hours (5). Buspirone exhibits linear kinetics following administration of single 10 to 40 mg doses (16). At higher doses given as multiple dosing, a nonlinear kinetic also was observed. However, it is unknown at what dose the nonlinearity starts. Although food increases the bioavailability of buspirone by decreasing first pass metabolism, the total amount of drug (changed and unchanged) in plasma is not affected (17,18).

II. IN VIVO BIOEQUIVALENCE STUDIES [2]

A. Product Information

1. FDA-designated reference product: BuSpar (Bristol-Myers Squibb) 15-mg tablets.

2. Batch size: The test batch or lot should be manufactured under production conditions and be of a size at least 10 percent that of the largest lot planned for full production or a minimum of 100,000 units, whichever is larger.

3. Potency: The assayed potency of the reference product should not differ from that of the test product by more than 5 percent.

B. Types of Studies Recommended

1. A single-dose, randomized, fasting, two-treatment crossover study under fasting conditions comparing equal doses of the test and reference products.

2. A single-dose, randomized, three-treatment, three-period, six-sequence, crossover, limited-food-effects study comparing equal doses of the test and reference products when administered immediately following a standard breakfast.

C. Recommended Protocol for Conducting a Single-Dose Bioequivalence Study under Fasting Conditions

Objective: To compare the rate and extent of absorption of a generic formulation with that of a reference formulation when given in equal doses.

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[2] The sponsoring firm is advised that an investigational new drug application may be required if dosing levels exceed those recommended in the official labeling. Please refer to 21 CFR 312.2, 320.31(b)(1).

Design: A single-dose, randomized, two-period, two-treatment, two-sequence crossover study using a sufficient number of subjects to ensure adequate statistical results and with one week washout period between phases I and II, or a single-dose, randomized, fasting, two-treatment, four-period, four-sequence replicate design crossover study in fasting subjects with one week washout period between phases of dosing. Equal numbers of subjects should be randomly assigned to the dosing sequences. Before the study begins, the proposed protocols should be approved by an institutional review board.

Facilities: The clinical and analytical laboratories used for the study should be identified along with the names, titles, and curriculum vitae of the medical, scientific, and analytical directors.

Subjects: The sponsor should enroll a number of subjects sufficient to ensure adequate statistical results. Subjects should be healthy volunteers, 18 to 50 years in age, and within 10 percent of ideal body weight for height and build (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Subjects should be selected on the basis of acceptable medical history, physical examination, and clinical laboratory test results. Subjects with any current or past medical condition that might significantly affect their pharmacokinetic or pharmacodynamic response to the administered drug should be excluded from the study. Written, informed consent must be obtained from all study subjects before they are accepted into the studies.[3]

Procedures: Following an overnight fast of at least 10 hours, subjects should be administered a single dose (2 x 15 mg tablets) of the test or reference product with 240 mL of water.

Restrictions: Study participants should observe the following restrictions:

1. Water may be allowed except for one hour before and after drug administration when no liquid should be permitted other than that needed for drug dosing.

2. Subjects should fast for at least four hours after administration of the test or reference treatment. All meals should be standardized during the study.

3. No alcohol or xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

[3]Please refer to 21 CFR 50.

4. Subjects should take no prescription medications beginning two weeks and no over-the counter medications beginning one week before drug administration and until after the study is completed.

Blood Sampling: Venous blood samples should be collected predose (0 hours) and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 7.0, 8.0, 12, and 24 hours postdose. Plasma should be separated promptly and immediately frozen until assayed. Following a washout period of at least one week, subjects should begin the second phase of the study.

Analytical Methods: Buspirone and its active metabolite, 1-pyrimidinylpiperazine (1-PP), should be assayed using a suitable method fully validated with respect to adequate sensitivity, specificity, linearity, recovery, and accuracy and precision (both within and between days). Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined. Chromatograms of the analysis of the unknown samples, including all associated standard curve and quality control chromatograms, should be submitted for one-fifth of the subjects, chosen at random. The sponsor should justify the rejection of any analytical data and provide a rationale for selection of the reported values. Successful completion of the studies described in this guidance is dependent on the use of an assay with a sufficient level of sensitivity to measure both buspirone and its active metabolite.

Statistical Analysis of Pharmacokinetic Data (Plasma): See Division of Bioequivalence guidance, Statistical *Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design or Replicated Treatment Designs*.

Clinical Report and Adverse Reactions: Subject medical histories, physical examination reports, and all incidents of possible adverse reactions to the study formulations should be reported.

D. Limited-Food-Effects Study

A limited-food-effects study should be performed in the same manner as the single-dose fasting study, with the following exceptions:

Procedures: Equal numbers of subjects should be assigned to each of the six dosing sequences possible in a three-treatment, three-period study design. Each subject will receive the following treatments:

Treatment 1: Generic product, buspirone HCl (2 x 15-mg tablets) administered after a standard breakfast.[4]

Treatment 2: Reference product (BuSpar), (2 x 15-mg tablets) administered after a standard breakfast.

Treatment 3: Generic product, (2 x 15-mg tablets) administered under fasting conditions.[5]

Following a ten-hour fast, subjects receiving treatments 1 and 2 should be served a standard breakfast. The subjects should have thirty minutes to finish the entire breakfast, then be immediately dosed with 2 x 15-mg tablets of the test or reference product with 240 mL of water. Subjects receiving Treatment 3 should be dosed with 2 x 15-mg tablets of the test product with 240 mL of water only. The same lots of the test and reference products used in the study under fasting conditions should be used in the food study. No other food should be allowed for at least four hours postdose. Water may be allowed after the first hour. Subjects should be served scheduled standardized meals throughout the study.

Statistical Analysis: In general, a comparable food effect will be assumed provided the AUC_{0-T}, $AUC_{0-\infty}$, and C_{max} mean values for the test product differ no more than 20 percent from the respective mean values obtained for the reference product in this study.

Retention of Samples: The laboratory conducting the bioequivalence tests should retain an appropriately identified reserve sample of the test product and the reference standard used to perform the in vivo bioequivalence study for approval of the application. Each reserve sample should consist of at least 200 dosage units. For more information please refer to 21 CFR 320.32.

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[4] Thirty minutes before drug administration, each subject should consume a standardized, high fat content meal consisting of:

One buttered English Muffin
One fried egg
One slice of American cheese
One slice of Canadian bacon
One serving of hash brown potatoes
Eight fluid oz. (240 mL) of whole milk
Six fluid oz. (180 mL) of orange juice

[5] For additional guidance in performing the food effect study for buspirone, please refer to the guidance for industry, *Food-Effect Bioavailability and Bioequivlence* (draft, 10/1997), once it has been finalized.

III. IN VITRO TESTING

A. Dissolution Testing

Conduct dissolution testing on 12 dosage units of the test product versus 12 units of the reference product. The biostudy lots should be used for those product strengths tested in vivo. Because no official USP dissolution method is currently available for buspirone hydrochloride tablets, the FDA dissolution method should be followed. The following method and tolerances are currently recommended for this product:

Apparatus:	USP XXIII apparatus II (Paddle)
RPM:	50 RPM
Medium:	0.01N HCl at 37°C
Volume:	500 mL
Sampling Times:	10, 20, 30 and 45 minutes
Tolerance (Q):	NLT 80 percent in 30 minutes
Analytical:	As per USP XXIII, if available, or other validated method

The percent of the test and reference product dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

B. Content Uniformity Test

Content uniformity testing on the test product lots should be performed as described in USP XXIII.

IV. WAIVERS

Waiver of in vivo bioequivalence study requirements for the 5-mg and 10-mg tablets of the generic product may be granted per 21 CFR 320.22(d)(2) provided *both* of the following conditions are met:

A. The 5-mg and 10-mg tablets are proportionally similar in both active and inactive ingredients to the 15-mg tablet that has demonstrated bioequivalence to the listed reference (15 mg) product in vivo.

B. The 5-mg and 10-mg strengths of the generic product meet the specified dissolution testing requirement.

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